Remarks:

Reconsideration and withdrawal of the rejections set forth in the Office action dated June 27, 2005 are respectfully requested.

I. Amendment to the claims

Independent claims 1 and 3 were amended to include, and newly added claim 41 includes, the limitations that:

(a) the cell line of the claim has been transformed with a first expression vector comprising a coding sequence for an anti-apoptotic protein operably linked to a first promoter, and a second expression vector comprising the coding sequence for PKR operably linked to a second promoter; and

(b) the transformed cell line being characterized by a level of interferon-alpha production that is significantly greater than the level of a control cell line transformed with PKR alone when the transformed cell line and the control line are grown under cell culture conditions of interferon-alpha production induced by the addition of Sendai virus.

Support for limitation (a) is found, for example, in originally presented claim 5, when considered with the limitations of originally presented claim 3, and more generally, in Section VII on page 25-29 and in Example II on pages 35-36. Support for limitation (b) is found, for example, on page 37, line 13-16.

No new matter has been added by these amendments.

II. Rejections under 35 U.S.C. §103(a)

Claims 1-3, 5-8, 11, 25, 26, 29, 31-34, 37, 39, and 40 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Dixit (U.S. Patent No. 6,159,712), Lau et al., (U.S. Patent No. 6,159,712) and Suzuki et al. (Derwent Abstract XP-02170158). This rejection is respectfully traversed in view of the amendments to the claims and following remarks.

A. The invention

The present invention, as embodied in claim 1, is directed to a human cell line for use in producing one or more cytokines. The cell line has been transformed to express both a gene for PKR and a gene for an anti-apoptotic protein, and it is capable of producing levels of cytokine in culture, e.g., interferon-alpha, that are several fold greater than that produced by an untransformed cell line or a cell line transformed with the PKR gene alone.

The invention also includes a method of producing such a cell line (independent claim 3), and a method of using the cell line for cytokine production (independent claim 41).

The problem addressed in the invention is further enhancing the levels of cytokine that can be induced in a mammalian cell line transformed to over-express PKR. The invention is based, in part, on the discovery that a cell line which over-expresses PKR and also expresses an anti-apoptosis protein can be induced to significantly higher levels of cytokine production than is achieved with cells transformed to over-express PKR alone.

B. The cited prior art

Dixit describes a method for preventing or inhibiting apoptosis in a cell. The method includes introducing a nucleic acid coding for CrmA or a nucleic acid coding for a gene product having CrmA biological activity. The invention is also directed towards compositions and methods for maintaining the viability of T cells in an HIV-infected individual. (column 1, lines 65-66 and column 2, lines 1-15). This reference is not concerned with the problem of enhancing levels of cytokine production, and especially, enhancing levels of cytokine production in PKR overproducing cells.

Lau describes a method to increase production of interferon in an animal cell by increasing expression of PKR. The reference, in other words, inherently discloses the problem faced by the applicants, but in no way suggests a solution to the problem.

Suzuki et al. describe a method of improving production of a useful target material, such as antibodies, cytokines, etc., from a cell by inhibiting apoptosis of the cell by introducing into the cell an apoptosis inhibitor gene. Like the Dixit reference above, Suzuki does not recognize the problem of enhancing cytokine production in PKR over-expressing cells, nor does the reference suggest a solution to the problem, for the reasons discussed below.

C. Analysis

A *prima facie* case of obviousness under 35 U.S.C. §103(a) requires the following elements:

> (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the references.
>
> (2) there must be a reasonable expectation of success.
>
> (3) the prior art references when combined must teach or suggest all of the claim limitations. M.P.E.P. § 2143.

In addition, a claimed invention cannot be considered obvious if the cited art, taken either individually of in combination, fails to suggest the advantages achieved by the invention.

C1. No motivation to combine. The applicants' invention is directed to the problem of enhancing cytokine production in cells which have stimulated production of cytokines by virtue of over-expression of PKR, but which show reduced viability in culture, presumably due to elevated levels of produced cytokines. This problem would be inherent in Lau, but Lau does not recognize the problem nor offer any suggestion as to its solution.

One skilled in the art would not be motivated to look to Dixit for a solution to this problem since Dixit is not concerned with (i) cytokine production in cells, or (ii) the effect of enhanced cytokine production on cell viability. The reference therefore

fails to address the problem of enhancing cytokine production in PKR-overexpressing cells cultured under conditions of cytokine induction.

Similarly, one would not look to Suzuki for a solution to this problem. Suzuki discloses the use of an anti-apoptotic gene for enhancing the cellular production of a variety of proteins, including cytokines, but also including many other types of proteins, e.g., antibodies, vaccine, and cell growth factors. In other words, although Suzuki is concerned with stimulating protein production, including cytokines, the reference clearly fails to appreciate the potential of cytokine overproduction to limit cell viability. In fact, Suzuki does not actually show enhanced cytokine production in his disclosed method, so one skilled in the art, attempting to solve the problem of cytokine overproduction in mammalian cells, would not know whether this reference would even be relevant.

C2. No reasonable expectation of success. Nor would one have any reasonable expectation of success in combining Lau with Dixit and/or Suzuki. As mentioned above, Suzuki does not demonstrate that the method taught in the reference is actually effective in extending cell viability in cytokine-overproducing cells. In any event, given the complexity of cytokine production and its feedback on cells, there would be no expectation that the two different mechanisms, each capable of causing elevated cytokine production in cultured cells, would do anything other than aggravate the problem of cytokine overproduction seen with PKR over-producing cells.

C3. No suggestion of the advantages obtained by the combination. Nor do any of the cited references, taken individually or together, suggest the advantages achieved by the invention. As noted above, and included as a claim limitation in all of the pending claims, the transformation of cells with expression vectors for both PKR and an anti-apoptotic protein significantly enhances the level of cytokine obtained in culture relative to PKR-transformed cells alone when induced by Sendai virus. As seen in Fig. 5A of the application, this enhancement amounts to a several fold increase in interferon-alpha production over PKR-overproducing cells. Since neither Dixit nor Suzuki demonstrates any increase in cytokine production by

transforming cells with an anti-apoptotic gene, they cannot suggest that transformation with an anti-apoptotic gene would lead to a significance enhancement in cytokine production of a PKR-over-expressing cell line.

C4. Addressing the issue raised by *In re Kerkhoven*

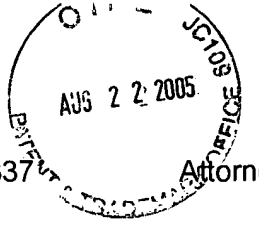
The Examiner states that "[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." M.P.E.P. §2144.06 (citing *In re Kerkhoven,* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (Office Action dated June 27, 2005, page 4). The Examiner states that "it would have been obvious ... to combine the anti-apoptotic protein, CrmA, with the PKR cell line, both of which are capable of overexpressing cytokines (products)." (Page 5).

The applicants submit that the logic of Kerkhoven is inapt to the present case. First of all, neither Dixit nor Suzuki demonstrates that transformation with an anti-apoptotic protein does, in fact, enhance cytokine production, as discussed above. Secondly, and more importantly, the loss of cell viability seen in Lau and first recognized by the applicants is due to overproduction of cytokines. It is not logical to assume, therefore, that employing a second mechanism that could further increase cytokine production would solve the problem addressed by the applicants' claimed invention,

In view of the above arguments, the currently amended claims cannot be considered obvious over a combination of Lau, Dixit, and/or Suzuki. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

III. Conclusion

In view of the foregoing, Applicants submit that the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested. The undersigned invites the Examiner to call (650) 838-4401 with any questions or comments. The Commissioner is hereby authorized



and requested to charge any deficiency in fees herein as needed to allow entry and consideration of this Amendment to Deposit Account No. 50-2207.

Respectfully submitted,
Perkins Coie LLP

Date: August 22, 2005

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